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# A NOVEL PATTERN OF MALE GERM CELL MUTAGENICITY INDUCED BY ETOPOSIDE IN MICE

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Etoposide (VP-16), a topoisomerase II inhibitor used in cancer therapy, is known to induces chromosome aberrations in somatic cells and mouse oocytes. We are reporting, for the first time, its effects on male germ cells. Following i.p. injection of 80 mg/kg, etoposide induced dominant lethal mutations (20-30%) in primary spermatocytes (22.5-27.5d) just prior to their entering meiotic division. There was also a slight (10-12%) increase in dominant lethal mutations induced in late differentiating spermatogonia/preleptotene spermatocytes (32.5-37.5d). No dominant lethals were induced in post meiotic spermatids, spermatozoa or sperm or in spermatogonial stem cells. This pattern of cell stage sensitivities has not been observed before. The cytogenetic mechanisms responsible for this pattern were investigated through examination of first(MMI)- and second(MMII)-meiotic metaphase chromosomes for structural aberrations (CA) and MMII chromosomes for numerical aberrations (AN) using fluorescence *in situ* hybridization (FISH) painting. Males were sacrificed at 6h, 16h, 40h, 64h and 10d after treatment and testes were prepared by a modified Meredith (1964) procedure. Preliminary examination of meiotic metaphases from one male per sacrifice time indicates extensive structural damage at both MMI (14-64% CA) and MMII (35-60% CA), which varied among stages in severity and type of damage. Damage observed at 6h was primarily centromeric fragments. Numerical damage (16-17% AN) was observed only in the 16h and 40h samples. The total chromosome damage seen in MMI and MMII cells correlates well with the level of dominant lethality. [Work was performed in part under the auspices of the US DOE by the Lawrence Livermore Natl. Lab. under contract W-7405-ENG-48]